International Journal of Infectious Diseases 38 (2015) 68–76

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis

Jens Vikse, Brandon Michael Henry *, Joyeeta Roy, Piravin Kumar Ramakrishnan, Krzysztof A. Tomaszewski, Jerzy A. Walocha

Department of Anatomy, Jagiellonian University Medical College, ul. Kopernika 12, 31-034 Krakow, Poland

ARTICLE INFO

Article history:
Received 3 May 2015
Received in revised form 18 June 2015
Accepted 9 July 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Procalcitonin
C-reactive protein
Meningitis
Diagnosis
Meta-analysis

SUMMARY

Objective: Clinically, it is often difficult to differentiate between bacterial and viral aetiologies in adults with suspected meningitis. Several studies have demonstrated the potential use of serum procalcitonin (PCT) in making this differentiation. The aim was to pool these studies into a meta-analysis to determine the diagnostic accuracy of PCT.

Methods: Major electronic databases were searched for articles studying the use of serum PCT in the differentiation of bacterial and viral meningitis in adult patients. No date or language restrictions were applied. Data analysis was performed using Meta-DiSc 1.4 and MIX 2.0.

Results: Nine studies (n = 725 patients) were included in the meta-analysis. Serum PCT was found to be a highly accurate test for diagnosing meningitis. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) for PCT were 0.90 (95% confidence interval (CI) 0.84–0.94), 0.98 (95% CI 0.97–0.99), 27.3 (95% CI 8.2–91.1), 0.13 (95% CI 0.07–0.26), and 287.0 (95% CI 58.5–1409.0), respectively. PCT was found to be far superior to C-reactive protein, which had a pooled DOR of only 22.1 (95% CI 12.7–38.3).

Conclusions: Serum PCT is a highly accurate diagnostic test that can be used by physicians for rapid differentiation between bacterial and viral causes of meningitis in adults.

1. Introduction

Bacterial meningitis (BM) is a significant cause of morbidity and mortality worldwide, with 1.2 million cases per year, resulting in 135 000 deaths.[1] Due to the high mortality rate and potential neurological sequelae in survivors, there is an urgent need for rapid diagnosis with near 100% sensitivity.[2] Cerebrospinal fluid (CSF) analysis is the current gold standard for the diagnosis of BM, along with biomarkers such as C-reactive protein (CRP) and white blood cell count (WBC). However, none of these tests achieve 100% sensitivity and confer a high enough specificity to distinguish between bacterial and viral meningitis (VM).[2]

CRP has traditionally been used as the biomarker for inflammation. However, CRP may show a delayed increase during the course of bacterial infection, resulting in false-negative tests in the early stages of the disease.[3–6] CRP can also be elevated in viral infections, limiting its ability to discriminate between bacterial and viral aetiologies of meningitis.[7] Procalcitonin (PCT) is now considered to be the best candidate to replace CRP due to its high diagnostic accuracy in various infectious pathologies, including sepsis, acute infectious endocarditis, and pancreatitis.[8] Fibronectin, interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-α) have also been proposed as potential biomarkers, but have not thus far been accepted widely for clinical use.[9]

Normal PCT levels in healthy individuals are <0.1 ng/ml, and levels increase dramatically in response to bacterial infection.[10] It has been hypothesized that this increase is due to the overexpression of the CALC-1 gene and increased release of PCT from various tissues in response to bacterial endotoxins and inflammatory cytokines such as TNF-α, IL-6, and IL-1β.[8,11,12] Unlike CRP, PCT has not been reported to be elevated in viral infections, thus conferring it the important ability to distinguish easily between bacterial and viral aetiologies.[13]

PCT also demonstrates utility in the early diagnosis of meningitis by rising after 4 h, peaking at 6 h, and remaining elevated over 24 h.[14,15] This is in contrast to CRP, which rises over 6–12 h and peaks at 24–48 h.[16,17] This delay in diagnosis, combined with the traditional 72-h wait for the results of Gram

* Corresponding author. Tel.: +48 795 677 090.
E-mail address: bmhenry55@gmail.com (B.M. Henry).

http://dx.doi.org/10.1016/j.ijid.2015.07.011

stains, often results in patients receiving empiric antibiotic therapy.[18,19] This can lead to potential adverse effects, increased health care costs, and an increased risk of nosocomial infection.[20–22]

Several studies have attempted to study the diagnostic accuracy of PCT in differentiating between BM and VM in adult patients.[23–31] The reported results of these studies are varied and a consensus has yet to be reached on the diagnostic value of PCT in meningitis.

The aim of this study was to pool and analyze the results of all the reported studies to determine the true diagnostic accuracy of PCT in adult patients with suspected meningitis.

2. Methods

2.1. Search strategy

In accordance with the PRISMA guidelines, a systematic literature search of the major electronic databases including PubMed, Scopus, EMBASE, Science Direct, Web of Science, and the Cochrane Library was performed to identify studies eligible for the meta-analysis. The search was specifically tailored to each of the electronic databases. Search terms included procalcitonin, PCT, S-PCT, ProCT, meningitis, and meningism. No date or language restrictions were set. Case reports, letters to the editor, and conference posters and abstracts were searched, but not included in the meta-analysis.

2.2. Selection of studies

Studies were eligible for inclusion in the meta-analysis if they (1) investigated the diagnostic accuracy of PCT in adult patients with suspected meningitis to distinguish between bacterial and viral aetiologies, (2) measured serum PCT on admission, and (3) reported data necessary to construct 2 × 2 tables (true-positives, false-positives, false-negatives, true-negatives). Studies were excluded if they (1) reported incomplete data or did not provide data necessary to construct 2 × 2 tables, (2) did not compare BM vs. VM, (3) had a poor methodological quality as determined using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, (4) studied exclusively paediatric populations, or (5) only measured the levels of PCT in CSF. Three authors (J.V., B.M.H., and P.K.R.) independently assessed each full-text article for inclusion in the analysis. Disagreements were resolved by a consensus among the authors. When necessary, articles were translated from their original text into English for further review by medical professionals who are native English speakers and fluent in the language of the original text.

2.3. Data extraction

Two authors (J.V. and J.R.) independently extracted data from the selected studies. Extracted data included sample size, mean age, PCT and CRP cut-offs, sensitivity, specificity, testing method, time of measurement, serum levels of PCT and CRP, and definitions of BM. Two by two tables were then constructed to calculate values of true-positives, false-positives, false-negatives, and true-negatives, to be pooled into the meta-analysis. In the case of studies that reported multiple cut-offs with sensitivities and specificities, the cut-off with the highest Youden's J statistic was used in the meta-analysis.[32] In the case of any discrepancies in the data, the authors were contacted by e-mail for clarification.

2.4. Quality assessment

Methodological quality was assessed with the QUADAS-2 tool.[33] This tool assesses risk of bias and applicability through a series of signalling questions related to methodological quality of the study. Risk of bias is assessed in four domains – patient selection, index test, reference standard, and flow and timing. Applicability is assessed by the first three of the aforementioned domains. Each domain was ranked as high risk, unclear risk, or low risk individually by two authors (J.V. and J.R.).

2.5. Statistical analysis

The statistical analysis was performed using Meta-DiSc 1.4 and MIX 2.0 by one of the authors (B.M.H.). Using a random-effects model, the pooled sensitivities, specificities, positive likelihood ratios (LR+), negative likelihood ratios (LR−), and diagnostic odds ratios (DOR) were calculated. Summary receiver operating characteristic (SROC) curves were generated and the area under the curve (AUC) and Q^* index (the point on the SROC curve where sensitivity and specificity are equal) were then calculated appropriately. Heterogeneity was assessed using the Higgins I^2 test, with values of 25%, 50%, and 75% indicating low, moderate, and high degrees of heterogeneity, respectively. The threshold effect was measured using Spearman's correlation coefficient.[34] In order to further explore heterogeneity, meta-regression was performed using a single covariate with logDOR as the dependent variable. To assess publication bias, an asymmetrical funnel plot was constructed. Due to the current lack of accurate and reliable tests for publication bias in diagnostic studies, no other assessments were performed.[35]

3. Results

3.1. Study identification

An overview of the study identification process is given in Figure 1. Through database searching, 2379 articles were initially

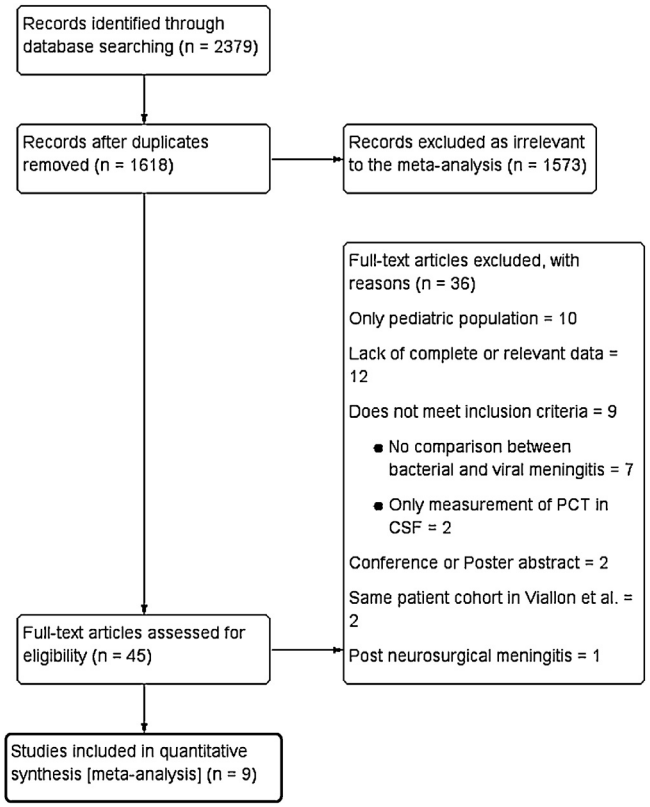

Figure 1. Flow chart of study identification, evaluation, and inclusion in the meta-analysis.

Table 1
Characteristics of studies included in the meta-analysis

Study	Population	Design	Mean age, years	Cases (*n*)		Biomarkers tested	Cut-off (PCT, ng/ml; CRP, mg/dl)	Sensitivity (%)	Specificity (%)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	PCT assay
				BM	VM									
Abdelkader 2014[23]	Egyptian	Prospective	39	16	24	PCT	1.2	68.8	83.3	11	4	5	20	RayBio Human Procalcitonin ELISA Kit
Jereb 2001[24]	Slovenian	Prospective	55	20	25	PCT	0.5	90	100	18	0	2	25	LUMItest (BRAHMS Diagnostika, Berlin, Germany)
						CRP	5	90	92	18	2	2	23	
Knudsen 2007[25]	Danish	Prospective	36.1	10	12	PCT	0.25	90	92	9	1	1	11	Kryptor PCT test (BRAHMS, Saint-Quen, France)
						CRP	4	90	75	9	3	1	9	
Makoo 2010[26]	Iranian	Retrospective	46.3	19	31	PCT	0.5	100	87.09	19	4	0	27	VIDAS BRAHMS PCT Assay
Mo 2012[27]	Korean	Retrospective	54.9	20	43	PCT	1	90	100	18	0	2	43	VIDAS BRAHMS PCT Assay
						CRP	6	85	88	17	5	3	38	
Morales Casado 2014[28]	Spanish	Prospective	44	38	33	PCT	0.74	94.7	100	36	0	2	33	ELECSYS BRAHMS PCT
						CRP	9	67.5	86.3	26	5	12	28	
Ray 2007[29]	French	Prospective	52	18	133	PCT	2.13	87	100	16	0	2	133	Kryptor PCT test (BRAHMS, Saint-Quen, France)
						CRP	2.2	78	74	14	35	4	98	
Schwarz 2000[30]	German	Prospective	52	16	14	PCT	0.5	69	100	11	0	5	14	LUMItest (BRAHMS Diagnostika, Berlin, Germany)
						CRP	0.8	94	57	15	6	1	8	
Viallon 2011[31]	French	Prospective	55	35	218	PCT	0.28	97	100	34	0	1	218	Kryptor PCT test (BRAHMS, Saint-Quen, France)
						CRP	3.7	86	84	30	35	5	183	

BM, bacterial meningitis; VM, viral meningitis; PCT, procalcitonin; CRP, C-reactive protein; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

identified. After screening and removal of duplicates, 45 articles were assessed by full text for eligibility in the meta-analysis. Of the full text articles, nine were deemed eligible for the meta-analysis and 36 were excluded from the meta-analysis. Two studies by Viallon et al.[36,37] containing overlap of patient data reported in a later publication[31] were excluded. One study looking at the diagnostic accuracy of PCT in post-neurosurgical meningitis was also excluded.[38]

3.2. Study characteristics and quality assessment

The characteristics of the studies included are summarized in Table 1. A total of nine studies ($n = 725$ patients) – two retrospective[26,27] and seven prospective[23–25,28–31] – were included in the meta-analysis. Of the studies included, seven were in English, one in Spanish, and one in Korean. The papers were also from a wide geographical spectrum, including Egypt, Slovenia, Denmark, Iran, Korea, Spain, France, and Germany. Only studies on adult patients were included. The mean age in the studies ranged from 39 to 55 years.

All studies measured serum PCT levels upon admission in patients with suspected meningitis to distinguish between a bacterial or viral aetiology. The cut-off for PCT varied amongst the studies and ranged between 0.25 ng/ml to 2.13 ng/ml. PCT assay methods also varied between studies and included the LUMItest (BRAHMS Diagnostika, Berlin, Germany),[24,30] Kryptor test (BRAHMS, Saint Quen, France),[25,29,31] VIDAS BRAHMS PCT assay,[26,27] RayBio Human Procalcitonin ELISA Kit,[23] and ELECSYS BRAHMS PCT test.[28]

The reported sensitivities for diagnosing BM in the studies that measured PCT ranged from 68.8% to 100% and specificities ranged from 83.3% to 100%. Seven of the nine studies also measured CRP as a biomarker, with cut-off values ranging from 0.8 mg/dl to 9 mg/dl. The reported sensitivities of CRP ranged from 67.5% to 90% and specificities ranged from 57% to 92%.

Overall, the methodological quality among the studies included was good, and the risk of bias was low. The study quality assessment using the QUADAS-2 tool is summarized in Figure 2.

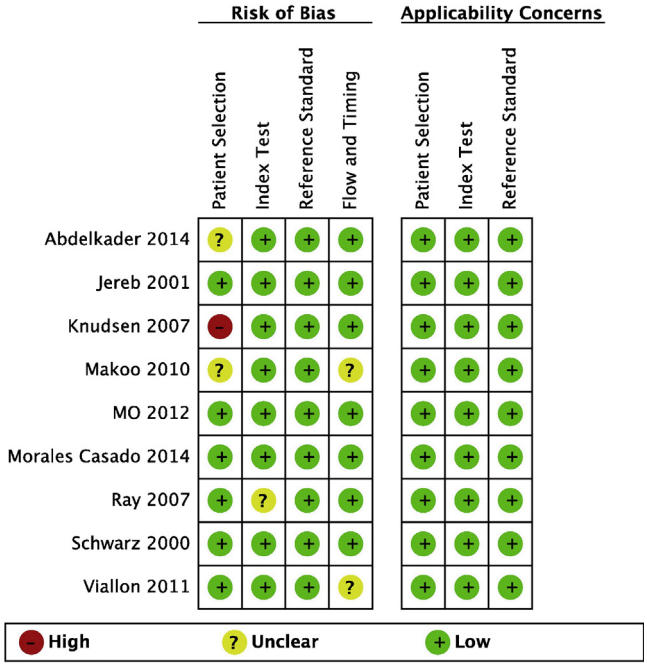

Figure 2. Summary of the QUADAS-2 assessment of the studies included.

3.3. Diagnostic accuracy indices

The results indicate that serum PCT is a highly accurate test for the detection of BM. The pooled sensitivity for PCT was 0.90 (95% CI 0.84–0.94), while the pooled specificity for PCT was 0.98 (95% CI 0.97–0.99) (Figure 3). The pooled LR+ was 27.3 (95% CI 8.2–91.1) and the pooled LR− was 0.13 (95% CI 0.07–0.26) (Figure 4A, B). PCT was found to be a very powerful diagnostic test, with a pooled DOR equal to 287.0 (95% CI 58.5–1409.0) (Figure 4C). A SROC curve was also constructed for PCT and the AUC was 0.97 (standard error (SE) = 0.03) and the Q^* index was 0.91 (SE = 0.04) (Figure 4D).

Seven of the nine studies included also assessed the diagnostic accuracy of CRP in order to compare it with the accuracy of PCT ($n = 635$ patients).[24,25,27–31] The pooled analysis showed that PCT is the more accurate and effective diagnostic test. The pooled sensitivity and specificity for CRP were 0.82 (95% CI 0.75–0.88) and 0.81 (95% CI 0.77–0.84), respectively (Figure 5). The difference in specificities indicates that PCT is far stronger at ruling in the diagnosis of BM as compared to CRP. The AUC for CRP was 0.89 (SE = 0.02) and the Q^* index was 0.83 (SE = 0.02). The pooled LR+ of CRP (4.2, 95% CI 2.8–6.0) was lower than that of PCT, but the pooled LR− of CRP (0.23, 95% CI 0.15–0.35) was similar to that of PCT. However, the DOR indicates the superiority of PCT, with the DOR of CRP equal to only 22.1 (95% CI 12.7–38.3).

3.4. Threshold effect and heterogeneity

Significant heterogeneity was detected for the pooled DOR of serum PCT ($I^2 = 66.2\%$). However, heterogeneity was also calculated for the pooled DOR of CRP and was found to be substantially lower than the heterogeneity associated with pooled PCT ($I^2 = 3.6\%$). To explore the source of heterogeneity, the threshold effect was assessed. The calculated Spearmen correlation coefficient for PCT was $r = -0.151$ ($p = 0.699$), indicating that the threshold effect was not the source of heterogeneity in the PCT analysis.

It was suspected that the cause of heterogeneity may have been variation in the type of serum PCT assay used in the studies. To further explore this hypothesis, a meta-regression was done to determine if the type of PCT testing assay was responsible for the heterogeneity. The calculated relative DOR (RDOR) was 3.42 (95% CI 1.49–7.81, $p = 0.01$), indicating that the PCT testing assay was a significant source of heterogeneity between studies. As such, a subgroup analysis was performed for each testing method used by at least two different studies in the analysis. Three studies ($n = 426$ patients)[25,29,31] used the Kryptor test (BRAHMS Diagnostika), which had the highest pooled DOR of all PCT assays (DOR 1125.2, 95% CI 77.4–16362.0), but also the most significant heterogeneity of the testing assays ($I^2 = 77.1\%$). Two studies ($n = 75$ patients)[24,30] used the LUMItest (BRAHMS Diagnostika) (DOR 146.9, 95% CI 17.1–1264.6, $I^2 = 0.0\%$) and two studies ($n = 113$ patients)[26,27] used the VIDAS BRAHMS PCT Assay (DOR 385.0, 95% CI 45.2–3281.2, $I^2 = 0.0\%$).

A subgroup analysis was also performed on three studies that reported a common serum PCT cut-off of 0.5 ng/ml ($n = 125$ patients).[24,26,30] The pooled sensitivity (0.87, 95% CI 0.76–0.94), specificity (0.94, 95% CI 0.86–0.984), and DOR (173.4, 95% CI 30.3–992.9) were all lower than in the general analysis. A second subgroup analysis was performed on two studies that had a lower PCT cut-off value ranging from 0.25 ng/ml to 0.28 ng/ml ($n = 275$ patients).[25,31] The pooled sensitivity (0.96, 95% CI 0.85–0.99) and specificity (0.99, 95% CI 0.98–1.0), as well as the DOR (945.3, 95% CI 10.2–87874.0), were higher than in the three studies with the higher common cut-off of 0.5 ng/ml.

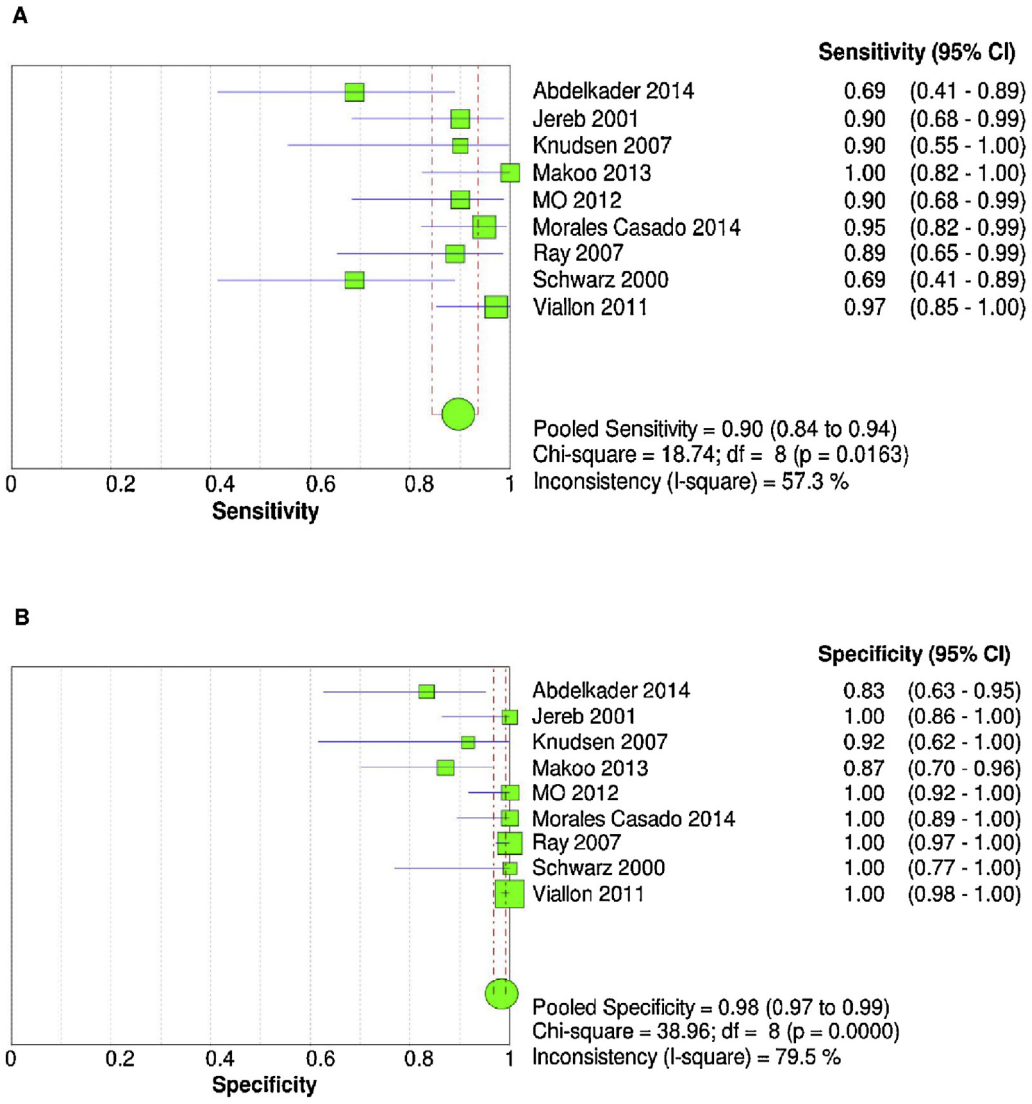

Figure 3. Pooled sensitivity (A) and specificity (B) for serum procalcitonin for the diagnosis of bacterial meningitis in adults.

3.5. Publication bias

Assessment for potential publication bias was performed using a funnel plot, which revealed asymmetry among the studies included (Figure 6).

4. Discussion

Procalcitonin is a 116-amino acid protein, initially discovered as the precursor molecule of the thyroid hormone calcitonin.[39] In recent years, however, it has become increasingly appreciated as a reliable marker of bacterial infection due to extensive non-thyroidal production in response to proinflammatory mediators such as TNF-α and IL-6.[11] Through a proposed cytokine-induced ubiquitous extrathyroidal upregulation of CALC-1 gene expression, bacterial infections induce a pervasive PCT release from hepatocytes, adipocytes, and various other parenchymal cells.[11] Because of the cytokine-induced recruitment of PCT-producing cells, it has been suggested that its serum levels may reflect disease severity.[40]

Due to the serious, time-sensitive nature and high mortality of BM, diagnostic tests with a high sensitivity and fast turnaround time are needed. This analysis demonstrates that serum PCT is a highly accurate diagnostic test for distinguishing between bacterial and viral aetiologies in patients with suspected meningitis. PCT was found to be a more specific than sensitive marker of BM. The pooled PCT specificity was 0.98 and LR+ was 27.3, indicating that PCT is a strong marker for ruling in BM in adult patients. This is compared to CRP, which had a specificity of 0.81 and LR+ of only 4.2. The likelihood ratio is a diagnostic test calculated from the sensitivity and specificity, and is an indicator of the value of performing a diagnostic test. It expresses the degree to which a diagnostic procedure modifies the probability of a disease. The range of LR is from 0 to infinity, therefore any values above or below 1, increase or decrease the likelihood of a disease, respectively.[41]

Pooled sensitivities between PCT and CRP were more similar, however the pooled sensitivity of PCT was still greater than that of CRP (0.90 vs. 0.82), albeit not significantly. AUC, an overall assessment of the quality of a diagnostic test, was 0.97 for PCT, as compared to 0.89 for CRP.

The true power of serum PCT is reflected in the DOR, which is a single indicator of the accuracy of a diagnostic test, combining data on both specificity and sensitivity.[42] It ranges in value from 0 to infinity, with higher values reflecting better test performance.[42]

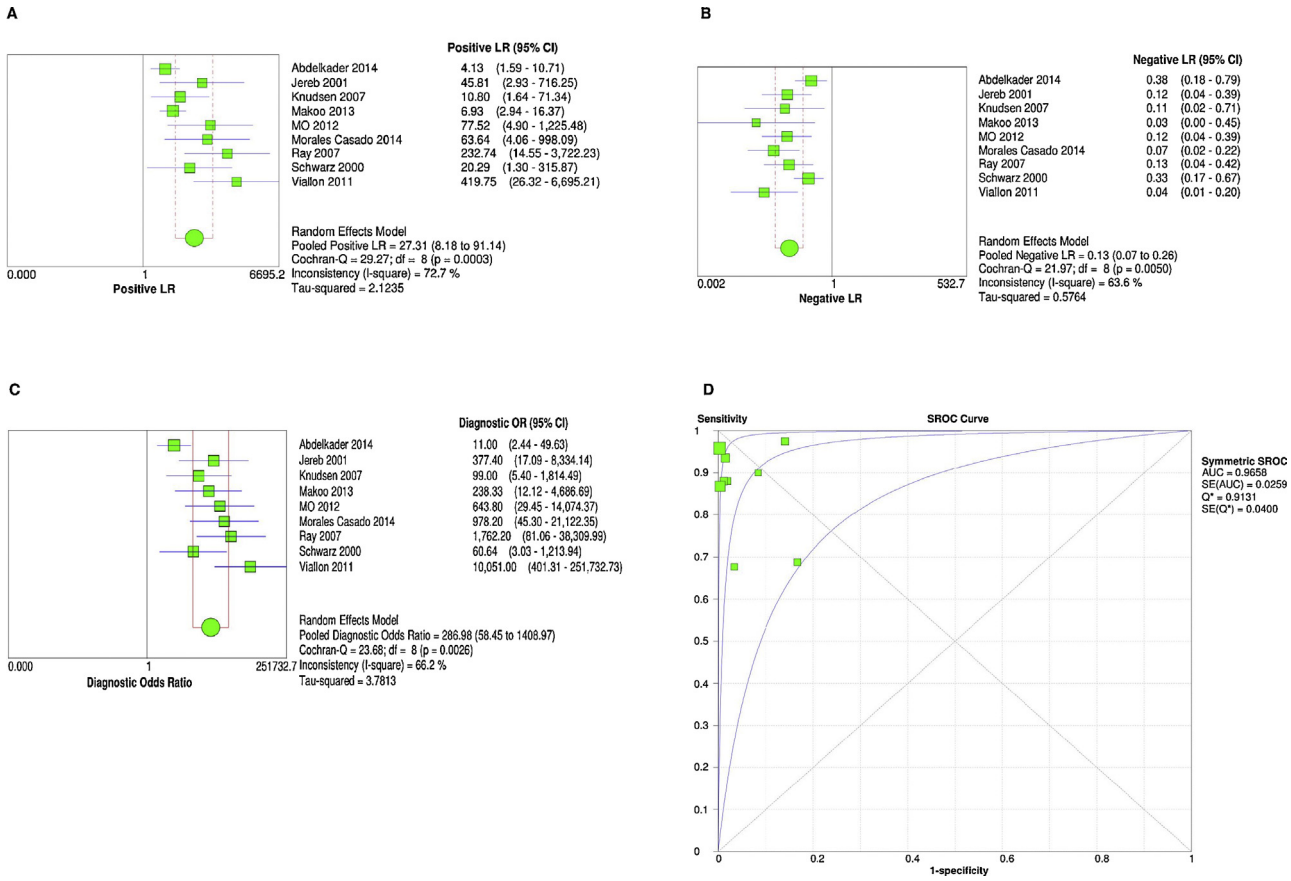

Figure 4. Pooled positive likelihood ratio (LR+) (A), negative likelihood ratio (LR−) (B), diagnostic odds ratio (DOR) (C), and summary receiver operating characteristic (SROC) (D) for serum procalcitonin for the diagnosis of bacterial meningitis in adults.

The DOR for PCT was 287.0, while the DOR for CRP was only 22.1. The strong DOR for serum PCT reflects its clinical utility in patients with suspected meningitis.

In suspected meningitis, the combined clinical history, physical examination findings, basic laboratory tests (such as WBC count), and lumbar puncture results of a patient form the gold standard for diagnosis. However, clinical symptoms and physical signs are often not present, and lack the ability to differentiate the aetiology of meningitis. Nakao et al. reported the sensitivities of fever, headache, vomiting, and rash for predicting pleocytosis in the CSF to be only 0.20, 0.91, 0.04, and 0.02, respectively.[43] Furthermore, the traditionally used meningeal signs, i.e., Kernig's sign, Brudzinski's sign, and nuchal rigidity, have a low diagnostic value.[44] Brouwer et al.[45] reported a pooled sensitivity of Kernig's sign in adults to be merely 0.11, while the reported pooled sensitivities of Brudzinski's sign and nuchal rigidity were 0.09 and 0.31, respectively. Due to the low sensitivities of physical signs, it is important to evaluate the entire clinical picture when formulating a differential diagnosis and determining further appropriate diagnostic tests.[45]

In order to confirm a clinical suspicion of meningitis and determine its aetiology, CSF analysis is considered the gold standard. However, it was found that the pooled serum PCT diagnostic accuracy indices in the present study were superior to those reported for CSF markers by Jereb et al.[24]. Their reported serum PCT sensitivity of 0.9 was found to be superior to all measured CSF parameters, including CSF leukocyte count (0.35), CSF polymorphonuclear leukocytes (0.45), CSF:blood glucose ratio (0.85), and CSF protein concentration (0.70). Their reported specificity of serum PCT of 1.0 was, however, comparable to the other CSF markers, which ranged from 0.96 to 1.0. This demonstrates that serum PCT allows for more accurate ruling out of BM as compared to traditional CSF markers.

As such, we recommend the use of a serum PCT assay to supplement the traditional gold standard combination of clinical history, physical examination, basic laboratory tests, and CSF analysis, in order to increase the overall diagnostic accuracy in differentiating the aetiology of suspected meningitis. Furthermore, owing to its high sensitivity and specificity, PCT may be helpful in situations where the conventional tests are unable to reach a conclusive diagnosis, such as in cases with non-conclusive CSF findings.

The level of PCT in the CSF has also been studied as a potential diagnostic biomarker of BM, albeit to a lesser degree than serum PCT. Three studies have assessed the diagnostic accuracy of PCT in CSF using the same cut-off value of 0.5 ng/ml.[24,26,40] The reported sensitivities ranged from 0.55 to 1.0, and the reported specificities in the studies ranged from 0.93 to 1.0. The mechanism by which the PCT concentration rises in the CSF during BM has been debated.[24,46] However, Konstantinidis et al.[40] showed that increased CSF PCT levels correlate with increased disease severity, duration, and mortality. Further studies are needed to confirm the efficacy of CSF PCT as a diagnostic marker of BM and its potential role as a prognostic marker of mortality.

In order to be widely implemented in the clinical setting, the economic implications of serum PCT and CRP testing must be considered. CRP is tested using a wide variety of inexpensive assays costing between USD $1 and $10.[47] However, according to a study by Nabulsi et al., routine CRP testing inflated hospital bills by USD $26 715.9, while failing to impact the decision-making process in a

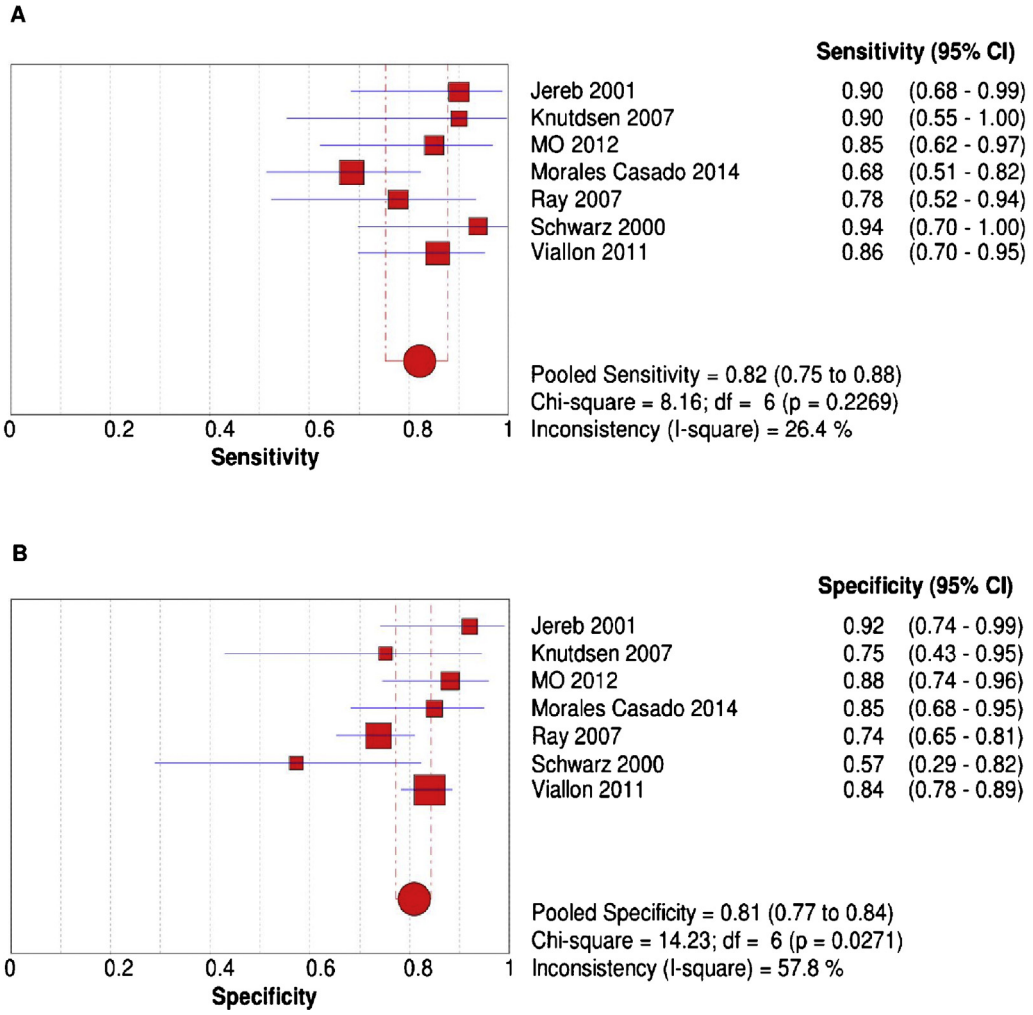

Figure 5. Pooled sensitivity (A) and specificity (B) for C-reactive protein for the diagnosis of bacterial meningitis in adults.

majority of cases.[48] The turnaround time for serum CRP assays is around 50 min, which can delay the initiation of immediate interventions.[49] On the other hand, PCT assays cost, on average, around USD $10 to 40,[47] and have significantly shorter turnaround times of around 20 min for the newer PCT testing assays such as Kryptor (BRAHMS Diagnostika).[50] This can be advantageous for the implementation of appropriate treatment, as well as for avoiding unnecessary empirical antibiotic therapy. For example, according to a review by Agarwal and Schwartz,[51] patients being treated for sepsis in the intensive care unit under PCT-guided interventions experienced a 28% to 31% reduction in the duration of antibiotic therapy.

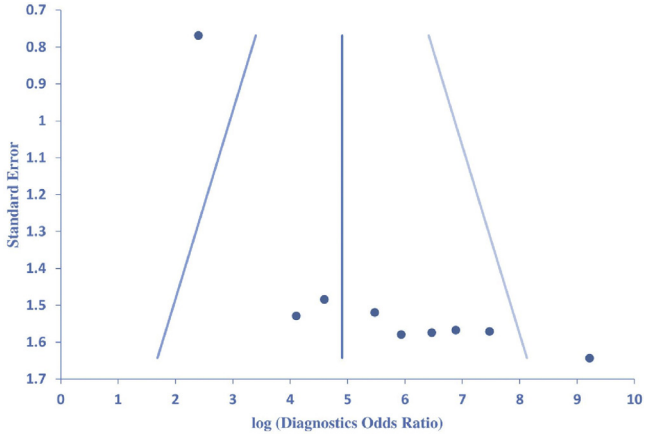

Figure 6. Funnel plot presenting study heterogeneity and potential for publication bias.

Due to the superior accuracy and power of PCT as compared to that of CRP, its clinical implementation can be a cost-effective tool in differentiating between BM and VM. The use of PCT to supplement the traditional gold standard would allow for the accurate and rapid differentiation of the aetiology of meningitis, early in the course of the disease, which could potentially limit the need for costly interventions such as blood cultures and empiric antibiotic therapy. The rapid confirmation of a viral aetiology would also reduce the costs of unnecessary hospitalization and the treatment of resulting potential nosocomial infections.

Furthermore, serum PCT levels, unlike those of CRP, have not been shown to be affected by non-steroidal anti-inflammatory drugs, steroids, or inflammatory comorbidities such as inflammatory bowel disease, systemic lupus erythematosus, or gout.[52–55] Additionally, PCT may potentially be useful in discriminating between bacterial and non-infectious aetiologies of meningitis. Neuro-Behçet's disease can mimic BM, presenting with acute meningeal symptoms and showing polymorphonucleic pleocytosis in the CSF.[56] In a case series of seven patients presenting with neuro-Behçet's disease by Suzuki et al.,[56] the authors found that all seven patients had elevated CRP levels, but none had an elevated

PCT level. These show yet additional benefits of using serum PCT as a biomarker, over CRP, in potential bacterial infections.

A few limitations on the clinical use of PCT should also be mentioned. The use of PCT to differentiate between BM and other causes of febrile encephalopathy due a bacterial aetiology, such as a brain abscess, is most likely limited, as PCT is often elevated in the case of most bacterial infections.[8] Furthermore, as PCT is also elevated in patients with bacterial pneumonia,[57] sepsis,[58,59] and other bacterial infections, the diagnostic use of PCT in patients presenting with acute meningitis in the presence of other bacterial infections is also potentially limited when compared to CSF analysis. Thus, physicians should take into account the entire clinical picture when formulating their diagnosis.

Additionally, PCT levels would be expected to decrease in patients receiving antibiotics prior to testing, thus giving misleading results.[60,61] Hu et al.[62] found that PCT levels decreased significantly 3 days after the initiation of antibiotic treatment in children with BM. Furthermore, the authors investigated how serum PCT levels correlated to disease severity.[62] They found patients with higher serum PCT levels had more severe clinical symptoms and increased mortality.[62] Additionally, in patients who did not experience clinical improvement after the initiation of antibiotic therapy, PCT levels did not decrease as significantly as compared to those who experienced clinical improvement.[62] Further studies should examine the use of PCT to assess prognosis, mortality, and the efficacy of antibiotic therapy in patients with BM, as well as how antibiotic therapy affects the use of PCT as a diagnostic marker.

This meta-analysis was limited by the number of studies available, the potential for publication bias, and the moderate heterogeneity between the studies included. In this analysis, the funnel plot did reveal asymmetry, however it is suspected that this was due to the limited number of studies included in the meta-analysis. Traditional publication bias assessments, such as Begg's test and Egger's test, are designed to assess bias in interventional studies, not diagnostic studies, and as such have low power and can give seriously misleading results.[35] This is due to the lack of proper determinants for measuring publication bias in diagnostic studies.[35] As such, the potential for publication bias in the studies included cannot be ruled out.

Heterogeneity in the present analysis appears to be due primarily to the type of PCT assay used in the study. The newest of the testing methods used in the studies, the Kryptor test (BRAHMS Diagnostika), had the highest pooled DOR of all the testing assays used in the analysis, but also had a moderate level of heterogeneity between the studies using this assay. However, with a rapid turnaround time of only 20 min and the high DOR, it represents an excellent assay that can be used clinically to assess PCT levels.[50] Despite the limitations of the meta-analysis, serum PCT is an excellent tool that can be used to enable quick and accurate differentiation between BM and VM in adults, and supplement the clinical history, physical examination, basic laboratory tests, and CSF analysis for a more accurate diagnosis.

Serum PCT cut-off values in the meta-analysis ranged from 0.25 ng/ml to 2.13 ng/ml. Interestingly, in subgroup analyses, a reduction in cut-off value from 0.5 ng/ml to a cut-off range of 0.25 ng/ml to 0.28 ng/ml, demonstrated an increase in sensitivity, specificity, and DOR from 0.87, 0.94, and 173.4 to 0.96, 0.99, and 945.3, respectively. It is suspected that this is due to the use of the Kryptor test (BRAHMS Diagnostika) PCT assay by both of the studies with the lower cut-off values, while no studies in the 0.5 ng/ml cut-off subgroup used this PCT assay. The increase in both sensitivity and specificity at this lower cut-off range as compared to the general analysis, increases the clinical utility of this test by increasing the ruling-out power of the PCT assay needed to accurately exclude BM. As such, the use of a low PCT cut-off of around 0.25 ng/ml with the Kryptor test (BRAHMS Diagnostika) PCT assay is recommended, which gives both the high sensitivity and high specificity needed clinically to accurately diagnose the cause of meningitis. However, further studies are required to determine the optimal cut-off values for the other PCT testing assays. Additionally, future studies should assess the diagnostic role of PCT specifically in suspected cases of meningitis with non-conclusive CSF findings, in cases of non-infectious meningitis, and in cases of meningitis caused by opportunistic pathogens such as *Mycobacterium tuberculosis*.

5. Conclusions

Serum PCT is a powerful diagnostic test for the assessment of suspected meningitis, allowing rapid differentiation between bacterial and viral aetiologies, and earlier initiation of appropriate and necessary therapies. The evidence suggests that while serum PCT offers a similar specificity to the traditionally used CSF markers of meningitis, it confers a higher sensitivity. Thus PCT, when used as a supplement to clinical signs and CSF analysis, allows for a more accurate overall diagnosis in patients with suspected meningitis. Lastly, this analysis indicates that PCT is a far superior diagnostic biomarker than the traditionally used marker of inflammation, CRP. The use of PCT serum assays in adult patients with suspected meningitis is therefore recommended.

Acknowledgements

This study and its publication was financed by the Jagiellonian University Faculty of Medicine KNOW funds. Krzysztof A. Tomaszewski was supported by the Foundation for Polish Science (FNP).

Conflict of interest: The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.07.011.

References

1. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis* 2002;**186**(Suppl 2):S225–33.
2. Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al. Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: a European multicenter case cohort study. *Arch Pediatr Adolesc Med* 2008;**162**:1157–63.
3. Peltola H, Jaakkola M. C-reactive protein in early detection of bacteremic versus viral infections in immunocompetent and compromised children. *J Pediatr* 1988;**113**:641–6.
4. Kono T, Otsuka M, Ito M, Misawa M, Hoshioka A, Suzuki M, et al. Negative C-reactive protein in children with bacterial infection. *Pediatr Int* 1999;**41**:496–9.
5. Himayun M, Ahmad S, Rasool A. Role of C-reactive protein in early onset neonatal sepsis. *Int J Pediatr Neonatol* 2009;**11**(2).
6. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. *Neonatology* 2012;**102**:25–36.
7. Hansson LO, Axelsson G, Linné T, Aurelius E, Lindquist L. Serum C-reactive protein in the differential diagnosis of acute meningitis. *Scand J Infect Dis* 1993;**25**:625–30.
8. Christ-Crain M, Muller B. Procalcitonin in bacterial infections—hype, hope, more or less? *Swiss Med Wkly* 2005;**135**:451–60.
9. Weirich E, Rabin RL, Maldonado Y, Benitz W, Modler S, Herzenberg LA, et al. Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. *J Pediatr* 1998;**132**:445–51.
10. Leclerc F, Leteurtre S, Noizet O, Dorkenoo A, Sadik A, Cremer R, et al. Procalcitonin as a prognostic marker in children with meningococcal septic shock. *Arch Dis Child* 2002;**87**:450.
11. Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-1 gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab* 2001;**86**:396–404.

12. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. *Endocrinology* 2003;**144**:5578–84.
13. Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. *J Lab Clin Med* 1999;**134**:49–55.
14. Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. *Arch Dis Child* 1999;**81**:417–21.
15. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* 1994;**79**:1605–8.
16. Mary R, Veinberg F, Couderc R. Acute meningitis, acute phase proteins and procalcitonin. *Ann Biol Clin* 2003;**61**:127–37.
17. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. *Intensive Care Med* 2000;**26**:79–87.
18. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;**39**:1267–84.
19. Feigin RD, McCracken GH, Klein JO. Diagnosis and management of meningitis. *Pediatr Infect Dis J* 1992;**11**:785–814.
20. Swingler G, Delport S, Hussey G. An audit of the use of antibiotics in presumed viral meningitis in children. *Pediatr Infect Dis J* 1994;**13**:1107–10.
21. Raymond J. Epidemiology of nosocomial infections in pediatrics. *Pathol Biol* 2000;**48**:879–84.
22. Parasuraman TV, Frenia K, Romero J. Enteroviral meningitis. Cost of illness and considerations for the economic evaluation of potential therapies. *Pharmacoeconomics* 2001;**19**:3–12.
23. Abdelkader NA, Mahmoud WA, Saber SM. Serum procalcitonin in Egyptian patients with acute meningitis and a negative direct cerebrospinal fluid examination. *J Infect Public Health* 2014;**7**:106–13.
24. Jereb M, Muzlovic I, Hojker S, Strle F. Predictive value of serum and cerebrospinal fluid procalcitonin levels for the diagnosis of bacterial meningitis. *Infection* 2001;**29**:209–12.
25. Knudsen TB, Larsen K, Kristiansen TB, Møller HJ, Tvede M, Eugen-Olsen J, et al. Diagnostic value of soluble CD163 serum levels in patients suspected of meningitis: comparison with CRP and procalcitonin. *Scand J Infect Dis* 2007;**39**:542–53.
26. Makoo ZB, Soltani HR, Hasani A, Makoo RB, Mashrabi O. Diagnostic value of serum and serum and cerebrospinal fluid procalcitonin in differentiation bacterial from aseptic meningitis. *Am J Infect Dis* 2013;**6**:93–7.
27. O M, Seo D, Kwak M, Shin J. Serum procalcitonin and C-reactive protein level as an early diagnostic marker of bacterial meningitis in the emergency department. *Ann Emerg Med* 2012;**60**:S22.
28. Morales Casado MI, Moreno Alonso F, Juárez Belaunde AL, Heredero Gálvez E, Talavera Encinas O, Julián-Jiménez A. Ability of procalcitonin to predict bacterial meningitis in the emergency department. *Neurologia* 2014 (Epub ahead of print).
29. Ray P, Badarou-acossi G, Viallon A, Boutoille D, Arthaud M, Trystam D, et al. Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative Gram-stained smear. *Am J Emerg Med* 2007;**25**:179–84.
30. Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W. Serum procalcitonin levels in bacterial and abacterial meningitis. *Crit Care Med* 2000;**28**:1828–32.
31. Viallon A, Desseigne N, Marjollet O, Birynczyk A, Belin M, Guyomarch S, et al. Meningitis in adult patients with a negative direct cerebrospinal fluid examination: value of cytochemical markers for differential diagnosis. *Crit Care* 2011;**15**:R136.
32. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding Youden index to discriminate individuals using pooled blood samples. *Epidemiology* 2005;**16**:73–81.
33. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Retisma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36.
34. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006;**6**:31.
35. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;**149**:889–97.
36. Viallon A, Zeni F, Lambert C, Pozzetto B, Tardy B, Venet C, et al. High sensitivity and specificity of serum procalcitonin levels in adults with bacterial meningitis. *Clin Infect Dis* 1999;**28**:1313–6.
37. Viallon A, Pouzet V, Zéni F, Tardy B, Guyomarch S, Lambert C, et al. [Rapid diagnosis of the type of meningitis (bacterial or viral) by the assay of serum procalcitonin]. *Presse Med* 2000;**29**:584–8.
38. Choi SH, Choi SH. Predictive performance of serum procalcitonin for the diagnosis of bacterial meningitis after neurosurgery. *Infect Chemother* 2013;**45**:308–14.
39. Maruna P, Nedelníková K, Gürlich R. Physiology and genetics of procalcitonin. *Physiol Res* 2000;**49**(Suppl 1):S57–61.
40. Konstantinidis T, Cassimos D, Gioka T, Tsigalou C, Parasidis T, Alexandropoulou I, et al. Can procalcitonin in cerebrospinal fluid be a diagnostic tool for meningitis? *J Clin Lab Anal* 2014;**29**:169–74.
41. Halkin A, Reichman J, Schwaber M, Paltiel O, Brezis M. Likelihood ratios: getting diagnostic testing into perspective. *QJM* 1998;**91**:247–58.
42. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003;**56**:1129–35.
43. Nakao JH, Jafri FN, Shah K, Newman DH. Jolt accentuation of headache and other clinical signs: poor predictors of meningitis in adults. *Am J Emerg Med* 2014;**32**:24–8.
44. Thomas KE, Hasbun R, Jekel J, Quagliarello VJ. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002;**35**:46–52.
45. Brouwer MC, Thwaites GE, Tunkel AR, Van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet* 2012;**380**:1684–92.
46. Gendrel D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. *Clin Infect Dis* 1997;**24**:1240–2.
47. Enguix A, Rey C, Concha A, Medina A, Coto D, Diéguez MA. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. *Intensive Care Med* 2001;**27**:211–5.
48. Nabulsi M, Hani A, Karam M. Impact of C-reactive protein test results on evidence-based decision-making in cases of bacterial infection. *BMC Pediatr* 2012;**12**:140.
49. Roubille M, Szymanowicz A, Cartier B, Albinet H, Carlier A, Goux A, et al. [Study on turnaround time of biological analysis in urgent need in hospital laboratories]. *Ann Biol Clin (Paris)* 2010;**68**:741–6.
50. Steinbach G, Rau B, Debard AL, Javourez JF, Bienvenu J, Ponzio A, et al. Multicenter evaluation of a new immunoassay for procalcitonin measurement on the Kryptor System. *Clin Chem Lab Med* 2004;**42**:440–9.
51. Agarwal R, Schwartz DN. Procalcitonin to guide duration of antimicrobial therapy in intensive care units: a systematic review. *Clin Infect Dis* 2011;**53**:379–87.
52. Thia KT, Chan ES, Ling KL, Ng WY, Jacob E, Ooi CJ. Role of procalcitonin in infectious gastroenteritis and inflammatory bowel disease. *Dig Dis Sci* 2008;**53**:2960–8.
53. Hugle T, Schuetz P, Mueller B, Laifer G, Tyndall A, Regenass S, et al. Serum procalcitonin for discrimination between septic and non-septic arthritis. *Clin Exp Rheumatol* 2008;**26**:453–6.
54. Chen DY, Chen YM, Ho WL, Chen HH, Shen GH, Lan JL, et al. Diagnostic value of procalcitonin for differentiation between bacterial infection and non-infectious inflammation in febrile patients with acute adult-onset Still's disease. *Ann Rheum Dis* 2009;**68**:1074–5.
55. Scire CA, Cavagna L, Perotti C, Bruschi E, Caporali R, Montecucco C, et al. Diagnostic value of procalcitonin measurements in febrile patients with systemic autoimmune disease. *Clin Exp Rheumatol* 2006;**24**:123–8.
56. Suzuki N, Mizuno H, Nezu M, Takai Y, Misu T, Kuroda H, et al. Procalcitonin might help in discrimination between meningeal neuro-Behçet disease and bacterial meningitis. *Neurology* 2009;**72**:762–3.
57. Pfister R, Kochanek M, Leygeber T, Brun-Buisson C, Cuquemelle E, Machado MB, et al. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. *Crit Care* 2014;**18**:R44.
58. Hoeboer SH, Van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect* 2015;**21**:474–81.
59. Ren H, Li Y, Han C, Hu H. Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: a meta-analysis. *Burns* 2015;**41**:502–9.
60. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med* 2011;**171**:1322–31.
61. Karlsson S, Heikkinen M, Pettilä V, Alila S, Vaisanen S, Pulkki K, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study. *Crit Care* 2010;**14**(6):R205. http://dx.doi.org/10.1186/cc9327.
62. Hu R, Gong Y, Wang Y. Relationship of serum procalcitonin levels to severity and prognosis in pediatric bacterial meningitis. *Clin Pediatr (Phila)* 2015. Epub ahead of print.